Disruption of the podosome adaptor protein TKS4 (SH3PXD2B) causes the skeletal dysplasia, eye, and cardiac abnormalities of Frank-Ter Haar Syndrome.

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Public Summary:

Scientific Abstract:
Frank-Ter Haar syndrome (FTHS), also known as Ter Haar syndrome, is an autosomal-recessive disorder characterized by skeletal, cardiovascular, and eye abnormalities, such as increased intraocular pressure, prominent eyes, and hypertelorism. We have conducted homozygosity mapping on patients representing 12 FTHS families. A locus on chromosome 5q35.1 was identified for which patients from nine families shared homozygosity. For one family, a homozygous deletion mapped exactly to the smallest region of overlapping homozygosity, which contains a single gene, SH3PXD2B. This gene encodes the TKS4 protein, a phox homology (PX) and Src homology 3 (SH3) domain-containing adaptor protein and Src substrate. This protein was recently shown to be involved in the formation of actin-rich membrane protrusions called podosomes or invadopodia, which coordinate pericellular proteolysis with cell migration. Mice lacking Tks4 also showed pronounced skeletal, eye, and cardiac abnormalities and phenocopied the majority of the defects associated with FTHS. These findings establish a role for TKS4 in FTHS and embryonic development. Mutation analysis revealed five different homozygous mutations in SH3PXD2B in seven FTHS families. No SH3PXD2B mutations were detected in six other FTHS families, demonstrating the genetic heterogeneity of this condition. Interestingly however, dermal fibroblasts from one of the individuals without an SH3PXD2B mutation nevertheless expressed lower levels of the TKS4 protein, suggesting a common mechanism underlying disease causation.